



## CRT Results: Patients Who Do Not Accept Radical Cystectomy But They Are Not Suitable For Bladder-Preserving Treatment

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### ABSTRACT

**Aim:** This study aimed to evaluate overall survival (OS) and disease-free survival (DFS) in patients with muscle-invasive bladder cancer (MIBC) who refused radical cystectomy and were not eligible for bladder-preserving treatment, and to identify prognostic factors affecting these outcomes under chemoradiotherapy (CRT).

**Materials and Methods:** A total of 71 patients with non-metastatic MIBC who underwent definitive CRT between 2010 and 2024 were retrospectively analyzed. Clinical findings and survival outcomes following CRT were evaluated.

**Results:** Among the 71 patients with bladder cancer, 90% were male and 10% were female. The median age was 72 years. Local recurrence occurred in 23 patients (32%), and distant metastasis was observed in 52 patients (73%). Male gender, concurrent chemotherapy including a platinum-based regimen, and a radiotherapy dose  $\geq 60$  Gy were identified as independent favorable prognostic factors for both OS and DFS. In addition, performance status was found to be an independent prognostic factor affecting OS.

**Conclusion:** Definitive chemoradiotherapy appears to be a reasonable treatment option for appropriately selected patients with muscle-invasive bladder cancer, particularly in those who decline radical cystectomy or are ineligible for trimodal bladder-preserving therapy.

**Keywords:** Chemoradiotherapy, bladder cancer, radical cystectomy, bladder-preserving treatment, prognostic factors, overall survival

## Radikal Sistektomiye Kabul Etmeyen Mesane Koruyucu Tedaviye De Uygun Olmayan Hastaların KRT Sonuçları

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### Öz

**Amaç:** Bu çalışmada kas invaziv mesane kanserinde radikal sistektomiye kabul etmeyen hastalarda koruyucu tedavi de uygun olmayan hastaların kemoradyoterapi (KRT) ile genel sağkalımı (OS) ve disease free survival (DFS) etkileyen prognostik faktörlerin araştırılması amaçlandı.

**Gereç ve Yöntem:** Çalışmaya, 2010-2024 yılları arasında metastatik olmayan kas invaziv mesane kanseri olan 71 hasta dahil edildi. Klinik bulgular ve KRT sonrası sağkalım analizi değerlendirildi.

**Bulgular:** Mesane kanserli 71 hastanın verileri incelendiğinde hastaların %90'ının erkek, %10'unun kadın olduğu saptanmıştır. Hastaların medyan yaşı 72 idi. 23 (%32) hastada lokal nüks ve 52 (%73) hastada uzak metastaz gelişmiştir. Erkek cinsiyet, eşzamanlı kemoterapi rejiminde platin kullanımı, RT dozunun  $\geq 60$  Gy olması hem OS'yi hemde DFS'yi etkileyen bağımsız iyi prognostik faktör olarak bulunmuştur. Ayrıca performans durumu da OS'yi etkileyen bağımsız iyi prognostik faktör olarak tespit edilmiştir.

**Sonuç:** Kas invaziv mesane kanseri özellikle radikal sistektomiye reddeden ya da mesane koruyucu trimodal tedaviye uygun olmayan hastalarda uygulanan definitif kemoradyoterapi uygun hastalarda makul bir seçenektir.

**Anahtar Kelimeler:** Kemoradyoterapi, mesane kanseri, radikal sistektomi, mesane koruyucu tedavi, prognostik faktörler, genel sağkalım, hastalısız sağkalım

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## Introduction

Bladder cancer is the fourth most common cancer in men worldwide, accounting for approximately 6% of all new cancer cases and 4% of cancer-related deaths.<sup>1,2</sup> At diagnosis, about 70–75% of cases present as non-muscle-invasive bladder cancer (NMIBC), 20–25% as muscle-invasive bladder cancer (MIBC), and approximately 5% as metastatic disease.<sup>3–6</sup> Around 90% of bladder cancers are histologically classified as urothelial carcinoma.

While most patients with NMIBC can be successfully treated with intravesical therapy following transurethral resection (TUR) of the tumor, radical cystectomy remains the standard treatment approach for MIBC.<sup>3</sup> Radical cystectomy involves the surgical removal of the bladder along with pelvic lymph node dissection and carries a significant risk of morbidity and mortality. Therefore, bladder-preserving treatment strategies are considered as alternatives in appropriately selected patients.<sup>5</sup>

Bladder-preserving trimodal therapy consists of maximal TUR followed by CRT and systemic chemotherapy (CT). This approach has shown promising outcomes in patients with good performance status, unifocal T2–T3 tumors, preserved renal function allowing for cisplatin use, and no evidence of obstructive uropathy or carcinoma in situ.<sup>6–8</sup> Trimodal therapy offers both oncological control and functional preservation, serving as a viable alternative to surgery.<sup>9</sup>

However, some patients either decline radical cystectomy for personal reasons or are medically unfit for surgery. Additionally, not all patients are suitable candidates for trimodal therapy. In this group, therapeutic options are limited, and there is no well-defined clinical management pathway.

The present study aims to evaluate the effects of definitive chemoradiotherapy on OS and DFS in patients with MIBC who are not candidates for radical cystectomy or trimodal bladder-preserving therapy and to identify prognostic factors associated with these outcomes.

## Materials and Methods

In this study, data from 71 patients with Bladder Cancer treated at the Oncology Center of Cumhuriyet University Faculty of Medicine between January 2010–December 2024 were retrospectively analyzed. Ethical approval for the study was granted by the Ethics Committee of Sivas Cumhuriyet University Faculty of Medicine (Date:15.5.2025, No: 2025-05/07). This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the local ethical committee (Sivas Cumhuriyet University Ethical Committee). Written informed consent could not be obtained due to the retrospective nature and anonymous data.

### Patient Selection

Female patients aged 18 years or older with histologically confirmed Bladder Cancer were included in the study. Patients with non-metastatic Bladder Cancer, Patients who had undergone radical cystectomy or were eligible for bladder-preserving trimodal therapy were excluded from the study.

A total of 71 patients diagnosed with invasive bladder cancer following TUR, who were either medically unfit for radical

surgery or refused radical cystectomy, were included in the study. Relevant laboratory and pathology results were retrieved from hospital records, while treatment follow-up data were obtained from clinical files. Patients who were eligible for bladder-preserving trimodal therapy or who underwent radical cystectomy were excluded from the study. Additionally, patients with distant metastases or those who received palliative radiotherapy were not included in the analysis.

### Data Collection

Clinicopathological data including age, sex, performance status, tumor stage, histopathological subtype, number of tumor foci, presence of hydronephrosis, lymph node status, treatment protocols, and survival outcomes were collected from the hospital information system and patient records. Performance status was assessed according to the Eastern Cooperative Oncology Group (ECOG) criteria. All patients were staged at the time of diagnosis according to the 8th edition of the American Joint Committee on Cancer (AJCC) staging system.<sup>10–11</sup>

OS was defined as the time from diagnosis to death or the last follow-up date. DFS was defined as the time from diagnosis to disease progression, recurrence, or death from any cause.

### Treatment Protocol

All patients underwent maximal TUR following evaluation by a multidisciplinary tumor board. Patients were stratified into two groups based on their Eastern Cooperative Oncology Group (ECOG) performance status: good performance (0–1) and poor performance ( $\geq 2$ ). Risk classification was based on tumor stage, tumor size, multifocality, presence of carcinoma in situ (CIS), and hydronephrosis, and was defined as follows:

Low risk: Stage T2–T3, tumor  $< 5$  cm, unifocal, no CIS, no hydronephrosis

High risk: Stage T4, tumor  $\geq 5$  cm, multifocal, presence of CIS and/or hydronephrosis

### Radiotherapy and Chemotherapy

Radiotherapy was delivered using conventional fractionation with either a linear accelerator (LINAC,  $n=28$ ; 78%) or TomoTherapy ( $n=8$ ; 22%). Treatment planning was performed using either the Eclipse 3D-conformal radiotherapy system (version 8.6, Varian Medical Systems, USA) or the Tomo HD VoLO system for intensity-modulated radiotherapy (IMRT).

According to the treatment protocol, the pelvic region (including obturator, internal, and external iliac lymph nodes and the entire bladder) received a total dose of 40–45 Gy. A boost dose was administered to the bladder to reach a total radiation dose of 60–66 Gy, while respecting organ dose constraints.

Concurrent chemotherapy consisted of weekly cisplatin (35 mg/m<sup>2</sup>), gemcitabine (400 mg/m<sup>2</sup>) or a combination regimen (cisplatin 75 mg/m<sup>2</sup> 1. day + gemcitabine 400 mg/m<sup>2</sup> 1. and 8. day). None of the patients underwent radical cystectomy following CRT.

### Statistical Analysis

All statistical analyses were conducted using SPSS version 23.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics (frequency, median, minimum, maximum) were used to summarize patient demographic and clinical characteristics.

Survival analyses were performed using the Kaplan-Meier method. Prognostic factors were assessed using univariate and multivariate Cox regression analyses. A p-value of <0.05 was considered statistically significant.

## Results

Analysis of data from 71 patients with bladder cancer showed that 90% were male and 10% were female. The median age of the patients was 72 years (range: 53–89). Comorbidities were present in 68% of the patients. Regarding tumor histology, 94% had urothelial carcinoma. In terms of staging, 63% were diagnosed with stage 2 disease, while 37% had stage 3–4 disease based on cystoscopy evaluation. Recurrence was observed in 32% of patients, and distant metastasis was noted in 27%. The demographic and clinical characteristics of the patients are summarized in Table 1.

### Overall Survival

Performance status ( $p = .001$ ), gender ( $p < .001$ ), radiotherapy (RT) dose (<60 Gy vs.  $\geq 60$  Gy;  $p = .041$ ), and the type of concurrent chemotherapy regimen (cisplatin vs. gemcitabine vs. combination;  $p = .011$ ) were found to

be statistically significant factors affecting OS. In contrast, tumor stage, tumor focality (unifocal vs. multifocal), presence of hydronephrosis, degree of tumor resection during TUR (complete vs. incomplete), post-CRT chemotherapy, and the type of radiotherapy device used (LINAC vs. TomoTherapy) were not statistically significant. The prognostic factors affecting patient survival are presented in Table 2. Male gender, good performance status, use of platinum-based concurrent chemotherapy, and a RT dose of  $\geq 60$  Gy were identified as independent favorable prognostic factors for overall survival.

### Disease Free Survival

Performance status ( $p = .049$ ), gender ( $p = .001$ ), radiotherapy dose (<60 Gy vs.  $\geq 60$  Gy;  $p = .041$ ), and the type of concurrent chemotherapy regimen (cisplatin vs. gemcitabine vs. combination;  $p = .041$ ) were identified as statistically significant factors influencing DFS. The prognostic factors affecting DFS are presented in Table 3.

Male gender, the use of platinum-based concurrent chemotherapy, and a radiotherapy dose of  $\geq 60$  Gy were found to be independent favorable prognostic factors for DFS.

Table 1. Clinical, and Pathological Characteristics of Patients

	Number of patients:n=71	%
Gender		
Male	64	90
Female	7	10
ECOG		
ECOG 0	37	45
ECOG 1	22	31
ECOG $\geq 2$	12	14
Patolojik Subtypes		
Uroepitelyal	67	94
Others	4	6
Grade		
Grade I	4	6
Grade II	2	3
Grade III	62	91
The Number of Tumor		
Unifocal	38	54
Multifocal	33	46
Hydronephrosis		
No	31	44
Yes	40	56
Stage		
Stage II	45	63
Stage III-IV	26	37
Node		
N0	55	78
N+	16	22
Distant Met		
No	52	73
Yes	19	27
Recurrence		
None	23	32
Present	48	68

ECOG PS: Eastern Cooperative Oncology Group performance status.

Table 2. Overall survival outcomes of patients.

	3-year survival (%)	5-year survival (%)	Median survival (months)	p value
Gender				
Male	40	30	29	<0.001
Female	-	-	7	
ECOG				
ECOG 0	39	28	29	0.001
ECOG 1	41	16	27	
ECOG ≥2	14	15	8	
The Number of Tumor				
Unifocal	35	21	27	0.579
Multifocal	37	29	27	
Hydronephrosis				
No	53	39	46	0.118
Yes	20	11	19	
Treatment				
Only RT	21	11	19	0.097
CRT	43	29	32	
RT schedule				
Konvansiyonel	39	27	27	0.517
SIB	34	0	15	
RT doses				
<60 Gy	25	14	19	0.041
≥60 Gy	53	45	59	
KRT Scheme				
Platinum	61	41	46	0.011
Gemcitabine	33	22	16	
Combine	0	0	7	
Stage				
Stage II	34	25	27	0.657
Stage III-IV	31	11	16	
<b>Multivariate analysis</b>	<b>HR</b>		<b>95% CI</b>	<b>p value</b>
Gender				
Male	RF			0.008
Female	7,14		1.67-30.53	
ECOG				
ECOG 0	RF			0.541
ECOG 1	0.81		0.42-1.56	
ECOG ≥2	3.49		1.56-7.81	
RT doses				
<60 Gy	RF			0.002
≥60 Gy	0.22		0.08-059	
KRT Scheme				
Platinum	1			0.007
Gemcitabine	3.46	1.41-8.55		
Combine	5.79	1.78-18.77		

ECOG PS: Eastern Cooperative Oncology Group performance status.

Table 3. Disease Free Survival Outcomes of Patients.

	3-year survival (%)	5-year survival (%)	Median survival (months)	p value
Gender				
Male	36	17	23	<b>0.001</b>
Female	-	-	7	
ECOG				
ECOG 0	35	21	27	<b>0.049</b>
ECOG 1	35	7	23	
ECOG $\geq 2$	15	0	7	
The Number of Tumor				
Unifocal	32	11	20	0.931
Multifocal	32	14	16	
Hydronephrosis				
No	42	19	27	0.245
Yes	24	12	16	
Treatment				
Only RT	16	37	19	0.579
CRT	11	18	16	
RT schedule				
Konvansiyonel	33	15	19	0.638
SIB	28	-	15	
RT doses				
<60 Gy	24	14	15	0.089
$\geq 60$ Gy	44	18	32	
KRT Scheme				
Platinum	51	26	42	<b>0.041</b>
Gemcitabine	27	13	14	
Combine	0	0	7	
Stage				
Stage II	32	16	27	0.436
Stage III-IV	26	10	14	
<b>Multivariate analysis</b>	<b>HR</b>		<b>95% CI</b>	<b>p value</b>
Gender				
Male	RF			<b>0.043</b>
Female	3.82		1.04-13.97	
RT doses				
<60 Gy	RF			<b>0.002</b>
$\geq 60$ Gy	0.22		0.08-059	
KRT Scheme				
Platinum	RF			0.101 <b>0.012</b>
Gemcitabine	1.90		0.88-4.13	
Combine	3.80		1.34-10.72	

ECOG PS: Eastern Cooperative Oncology Group performance status.

## Discussion

In patients with muscle-invasive bladder cancer who either refuse radical cystectomy or are not candidates for bladder-preserving trimodal therapy, treatment remains challenging. This difficulty is further exacerbated by the fact that these patients are often diagnosed at an advanced age. Bladder cancer is more commonly diagnosed in older adults, and it has been reported to be more frequent in women than in men.<sup>12</sup> In our study, 90% of the patients were male, with a median age of 72, which aligns with global epidemiological data on bladder cancer.<sup>12</sup>

In our study, a good performance status (ECOG <2), the use of platinum-based chemotherapy, and a radiotherapy dose of 60 Gy or higher were significantly associated with better outcomes in both OS and DFS. These findings are consistent with previous studies that highlight the role of performance status and aggressive treatment in the success of CRT.<sup>12-13</sup>

The Radiation Therapy Oncology Group (RTOG) has been investigating bladder-preserving treatments since the 1980s.<sup>14-17</sup> The RTOG has conducted a series of CRT studies using various chemotherapy agents. These studies have reported 5-year OS rates ranging from 49.5% to 71.75%.<sup>15-17</sup> A retrospective analysis of 475 bladder cancer patients treated with TUR + CRT (cisplatin, 5-

fluorouracil, paclitaxel, gemcitabine radiation dose of 64 Gy) between 1986 and 2013 showed a 5-year OS 57% and a 5-year DFS 66%. Advanced age was identified as an independent adverse prognostic factor for overall survival.<sup>16-17</sup>

Wujanto et al. evaluated 45 bladder cancer patients taht 21 (47%) applied CRT and 24 (53%) RT. Forty-two patients (93%) completed the planned treatment. In this study, performance status was identified as an important prognostic factor for survival.<sup>18</sup>

The BC2001 study showed that adding concurrent chemotherapy to radiotherapy improves local control and DFS.<sup>19</sup> Similarly, the other retrospective series, 5-year OS rates ranged from 50% to 60%.<sup>15-19</sup>

Although tumor multifocality, hydronephrosis, and tumor stage are recognized as significant prognostic factors in many studies, these parameters did not reach statistical significance in our multivariate analysis. This discrepancy may be attributed to differences in patient selection criteria and variations in the chemoradiotherapy protocols used.<sup>19</sup>

Our findings suggest that CRT, particularly when combined with platinum-based chemotherapy, may serve as an alternative to radical cystectomy in carefully selected patient populations. The treatment was well tolerated by the majority of patients, including elderly individuals, aligning with previously reported data in the literature.<sup>19</sup>

In many studies on bladder cancer, RT doses above 60 Gy have been used. Lee et al. reported a median dose of 58.6 Gy (range: 54–62.8 Gy) Hsieh et al. used a median dose of 64.8 Gy, and Korpics et al. used 60–66 Gy.<sup>20-22</sup> Similar to these studies, we administered a median dose of 60 Gy and 64 Gy to the pelvic region and bladder. CRT was well-tolerated by all patients in our study.

Bladder cancer stage is an important factor influencing both the disease course and survival rates. Several studies have been conducted on the stage of the disease and its prognosis, with varying results.<sup>12</sup> In our study, there was no significant difference in survival rates based on stage. DFS and OS were highest in Stage II, as nearly all these patients received CRT.

Hsieh et al. evaluated the outcomes of 19 bladder cancer patients treated with IMRT (N=9) or helical TomoTherapy (N=10). The median age of the patients was 80 years (range: 65–90). Regardless of whether the patients received concurrent chemotherapy, a median RT dose of 64.8 Gy was applied. The median survival for all patients was 21 months (range: 5–26 months). The 2-year OS was 26.3% for IMRT and 37.5% for helical TomoTherapy.<sup>21</sup> In contrast to this study, we did not find any statistically significant difference in survival between 3D-RT and TomoTherapy in our study. The 2-year OS rates were 32% for 3D-RT and 54% for TomoTherapy. Additionally, the 2-year OS rates in our study were slightly higher than those reported by Hsieh et al.

Korpics et al. compared RT and CRT in elderly bladder cancer patients using data from the National Cancer Database. The study involved 1369 bladder cancer

patients with clinical T2–4, N0–3, M0 disease, of whom 630 (46%) received CRT. The RT dose ranged from 60–70 Gy. The 2-year OS for patients who received CRT was 56%.<sup>22</sup>

In patients with locally advanced bladder cancer, concurrent cisplatin has been shown to enhance local control by acting as a radiosensitizer. In a study by Coppin et al., the complete response rate was 47% and the 3-year OS rate was also 47% in patients applied concurrent cisplatin with RT. The results were comparable to those of radical cystectomy.<sup>9</sup> In our study, patients treated concurrent cisplatin had better local control, distant recurrence-free survival, and overall survival outcomes compared to those treated with RT alone, concurrent carboplatin, or adjuvant chemoradiotherapy. In our study, age and gender did not show any prognostic impact on the target outcomes.

Most studies reporting definitive RT results in bladder cancer are retrospective. Therefore, it is difficult to obtain reliable data on the effect of performance status on treatment outcomes. However, even in studies based on chart reviews, performance status has been shown to be an important prognostic factor.<sup>22</sup> In our study, the statistical significance of performance status, gender, RT dose, and CRT regimen was demonstrated.

## Conclusion

This study shows that definitive CRT is an effective and feasible treatment option for patients with muscle-invasive bladder cancer who are not suitable for or refuse radical cystectomy. In particular, survival outcomes were significantly improved in patients with good performance status, those treated platinum-based chemotherapy, and those applying radiotherapy at doses of  $\geq 60$  Gy. However, when making treatment decisions for this patient group, all prognostic factors must be carefully considered. Prospective studies are needed to support our findings and standardize treatment protocols.

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